

## The Functions of BRCA1 in Mitochondria and Mitophagy

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Breast cancer 1 (BRCA1) gene is a major breast cancer susceptibility gene. Germline mutation in this gene predispose women to increase the risk for developing breast cancer, which are more often negative for estrogen receptor, progesterone receptor, and HER-2 (triple negative breast cancers, TNBC). BRCA1 tumor suppressor activity has been attributed to its nuclear localization, where it helps to maintain genome integrity. Recent studies showed that BRCA1 could localize on mitochondria, but the function of BRCA1 on mitochondria is still unknown.

Mitochondria are a double membrane-bound organelle containing its own independent genome. Mitochondrial DNA (mtDNA) stability is required for eukaryotic cells to assemble a functional electron transport chain. Somatic mutations in mtDNA have been demonstrated in various tumors, including breast cancer. Therefore, the maintenance of mtDNA integrity is important for keeping healthy of eukaryotic cells. This independently-maintained mtDNA relies on nuclear-encoded proteins that are imported into the mitochondria to carry out replication and repair processes. However, the mechanism that maintains mtDNA integrity is still not clear.

Two major repair pathways operate to repair DNA double-stranded breaks: homologous recombination (HR)-mediated repair and non-homologous end joining.

The HR-mediated repair uses a homologous template, and non-homologous end joining involves the direct ligation of DNA ends, which is sometimes accompanied by a loss of genetic information. BRCA1, as a tumor suppressor, could interact with different partners and maintain genomic stability through different pathways such as regulating HR-mediated repair, controlling cell cycle checkpoint, regulating DNA replication and protein ubiquitination. Our results showed that BRCA1 could translocate onto mitochondria under DNA damage condition,

which suggests that BRCA1 could some functions on maintaining mtDNA besides nuclear functions through HR-mediated repair or other pathways.

Mitophagy is a specialized autophagy pathway that mediates the clearance of damaged mitochondria by lysosomes, is important for mitochondrial quality control. Defective mitochondria, if left uncleared, can be a source of oxidative stress and compromise the health of the entire mitochondrial network. We found that BRCA1 could translocate on the mitochondria after mitochondrial damage, and BRCA1 deficiency caused more mitochondria damage, which suggest that BRCA1 could have some roles in regulating mitophagy. BRCA1 have an interaction with BARD1 to form heterodimer, which ensures genome stability through its role in protein ubiquitination. Broad activation of the ubiquitin-proteasome system by Parkin is critical for mitophagy. Therefore, it is suggested that BRCA1 could affect mitophagy through its ubiquitination function. In addition, mitochondrial dynamics, including mitochondrial fission/fusion and mitochondrial movement, is linked to mitophagy. During mitochondrial damage, mitochondrial could fission to fragmented mitochondria, which is mitophagy-competent mitochondria. BRCA1 may also mediate mitophagy through regulating mitochondrial dynamics after mitochondrial damage.

In summary, BRCA1, as a tumor suppressor, could localize on the mitochondria under DNA damage and mitochondrial damage condition, which suggest that BRCA1 could have some vital roles in maintenance of mitochondrial activity. It is well known that malignant cells typically have metabolic reprogramming, and show higher glycolytic rates and lower oxidative phosphorylation. Therefore, BRCA1 tumor suppressor activity is not only attributed to its nuclear localization, where it maintains nuclear genome integrity, but also to its mitochondrial localization, where it maintains mitochondrial functions.

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